CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	A convenient and mild chromatography-free method for the purification of the products of Wittig and Appel reactions
Authors	Byrne, Peter A.;Rajendran, Kamalraj V.;Muldoon, Jimmy;Gilheany, Declan G.
Publication date	2012-03-05
Original Citation	Byrne, P. A., Rajendran, K. V., Muldoon, J. and Gilheany, D. G. (2012) 'A convenient and mild chromatography-free method for the purification of the products of Wittig and Appel reactions', Organic & Biomolecular Chemistry, 10(17), pp. 3531-3537. doi: 10.1039/C2OB07074J
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://pubs.rsc.org/en/Content/ArticleLanding/2012/OB/c2ob07074j - 10.1039/C2OB07074J
Rights	© The Royal Society of Chemistry 2012
Download date	2024-03-29 02:17:56
Item downloaded from	https://hdl.handle.net/10468/7715

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Journal Name

Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A Convenient & Mild Chromatography-Free Method for the Purification of the Products of Wittig and Appel Reactions†

Peter A. Byrne,[a] Kamalraj V. Rajendran,[a] Jimmy Muldoon[a] and Declan G. Gilheany*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A mild method for the facile removal of phosphine oxide from the crude products of Wittig and Appel reactions is described. Work-up with oxalyl chloride to generate insoluble chlorophosphonium salt (CPS) yields phosphorus-free products for a wide variety of these reactions. The CPS product can be further converted into phosphine.

Phosphines and reagents derived from them are ubiquitous reagents in organic chemistry used, for example, in the Wittig reaction,[1] in Appel[2] and Mitsunobu[3] conditions and in the aza-Wittig reaction.[4] However the phosphine oxide by-product of these reactions poses significant problems, both of separation and disposal, leading to poor atom efficiency[5,6,7] and requiring complex procedures,[7,8] particularly for large-scale reactions. Disposal of phosphine oxide may be achieved by incineration to phosphorus pentoxide and hence calcium phosphate but more desirable is regeneration of the phosphine.[9] The BASF process for carotenoid synthesis[10] provides a good illustration of the issues. In it, the alkene product from a Wittig reaction is separated first from the bulk of the phosphine oxide by extraction with hydrocarbon solvents, and then scrubbed of remaining oxide in a second extractive column with aqueous alcohol. Regeneration of phosphine is achieved by reaction of oxide with phosgene to give triphenylphosphine dichloride (*vide infra*), which is then treated with elemental phosphorus to give triphenylphosphine and phosphorus trichloride, the latter being also a starting material for the former. Triphenylphosphine dichloride can also be converted to triphenylphosphine by mixing with finely divided aluminium metal in chlorobenzene, which forms a triphenylphosphine-aluminium trichloride complex that can be decomposed hydrolytically. Phase separation allows isolation of triphenylphosphine from the water-soluble aluminium-containing product, $Al(OH)Cl_2$.[9] These processes involve the handling of hazardous reagents and products, and are far from straightforward. Other methods for phosphine oxide removal include the addition of a hydrocarbon solvent and a carboxylic acid to the crude product, allowing separation of alkene (in organic phase) and phosphine oxide (in acid phase) by phase separation.[11] In some cases, the alkene can be crystallised, thus facilitating its separation from the other materials in the crude product.[12]

On a laboratory scale, phosphine oxide removal generally necessitates the use of column chromatography. This presents problems if the product is sensitive to decomposition or isomerisation through contact with the stationary phase or by light, or if it is sensitive to decomposition in air. For example, certain alkenes produced in Wittig reactions have been shown to be sensitive to isomerisation by light, or by contact with silica or alumina.[12] Thus, there is a strong imperative for the development of chromatography-free phosphine oxide removal. Reported methods addressing this need include modification of phosphonium ylides to furnish a phosphine oxide by-product that may be removed by aqueous work-up[13,14] and the use of water-soluble and hydrolytically stable ylides to allow reactions to be conducted in water, giving water-soluble phosphine oxide and insoluble alkene product, which precipitates and can be isolated by filtration.[15,16] An alternative approach involves polymer-supported ylides such as those of Westman[17] and Leung *et al.*[18] in which the ylide is generated *in situ* from a polymer supported phosphine. These reactions often have long reaction times and in some cases poor yield due to problems with polymer swelling. Some measure of success has been achieved for one-pot Wittig reactions involving *in situ* generation of stabilised ylides by the use of a bifunctional polymer containing phosphine and amine groups.[19] In all of the foregoing, the starting phosphine (free or polymer-bound) is either more expensive than triphenylphosphine, and/or must be synthesised by non-trivial routes. More seriously, the modified phosphonium entity may not have the same reactivity profile (e.g. may give different stereoselectivity in the Wittig), and the phosphorus substituents cannot easily be tuned to counter this without the undertaking of further onerous synthetic procedures.

A promising potential solution to the problem of phosphine oxide removal has been the development of processes that are catalytic in the phosphorus-containing entity. O'Brien, Chass and co-workers have recently reported the first catalytic Wittig reaction by using diphenylsilane to reduce the phosphine oxide, importantly leaving the carbonyl compound unaffected.[20] The reaction requires the use of a cyclic phosphine but, being catalytic, this is less problematic. Two protocols for carrying out Appel reactions that are catalytic in phosphine oxide have been reported recently.[21,22,23] In the process of Denton and co-workers, oxalyl chloride reacts with the oxide to give chlorophosphonium

salt (*vide infra*), which in turn reacts with alcohol to give alkoxyphosphonium salt, resulting in alkyl chloride and regenerating phosphine oxide. Denton *et. al.* have also developed a catalytic phosphine oxide-mediated dichlorination of epoxides using oxalyl chloride,[24] and an aza-Wittig reaction that is catalytic in phosphine oxide has also been reported.[25] A recent report focuses on utilising the phosphine oxide by-product of the Wittig reaction as a catalyst or co-catalyst (produced *in situ*) in a subsequent step of a tandem reaction sequence, thus improving the atom economy of the overall process.[6] The conversion of phosphine oxide to phosphine has also been realised by treatment with oxalyl chloride followed either by reaction of the resulting CPS (*vide infra*) with aluminium metal combined with a catalytic metal salt,[26] or by electrochemical reduction of the CPS.[27]

Finally, we note that it is not uncommon that the method used to remove phosphine oxide may result in isomerisation of a *Z*-alkene product of a Wittig reaction. This is the case, for example, in the catalytic version referred to above.[20] Isomerisation can be induced by the presence of acids,[28] strong bases,[29] the chromatographic stationary phase used,[12] the solvent, heat and sunlight. The *Z*-enones synthesised during this project were found to be extremely sensitive to isomerisation, such that samples containing only *Z*-enone isomerised to the *E*-isomer when simply allowed to stand, probably induced by light. For cases such as these, where the alkene cannot be stored or even exposed to chromatographic stationary phase, the development of a quick and easy chromatography-free method of separation of alkene and phosphine oxide is particularly important.

We now report a convenient work-up procedure for both Wittig and Appel reactions that allows such a rapid separation of the reaction product from phosphine oxide, and facilitates the reduction of the latter to phosphine. In the case of the Wittig reaction, the method is also successful in removing the aldehyde starting material and the conjugate acid of the ylide-generating base from the alkene and phosphine products of the process.

Our method is based on the aforementioned reaction of phosphine oxide with oxalyl chloride to generate chlorophosphonium chloride.[30] We were already interested in such salts because of their involvement in other chemistry in our laboratory.[31,32] They can also be generated by the reactions of phosphine with chlorine (in various solvents),[33,34,35,36] and phosphine oxide with sulfuryl chloride, methanesulfonyl chloride, thionyl chloride or trichloromethyl chloroformate.[30,32] The structure of the entity produced seems to depend heavily on the solvent. It adopts a chlorophosphonium chloride structure in acetonitrile and chlorinated solvents,[34] and a dichlorotriphenylphosphorane structure in benzene and diethyl ether.[34] During its hydrolysis in C_6D_6, both the ionic and covalent phosphorane forms co-exist.[36] A crystal structure of the compound produced by the reaction of Ph_3P and Cl_2 in dichloromethane showed it to have a dinuclear structure $[Ph_3PCl\cdots Cl\cdots ClPPh_3]Cl\cdot CH_2Cl_2$.[33] The compound has been observed by us and others to have limited solubility in diethyl ether (at room temperature)[34] and THF (with the small quantity that is soluble being in phosphorane form),[34] and very low solubility in alkane solvents and cold diethyl ether. This last point provides the basis of the new work-up procedure.

For the production of phosphorus-free alkene by the Wittig reaction, the reaction itself may be carried out using whatever starting materials and reaction conditions are required to give the desired product with the desired stereochemistry. For the reactions in this study, the phosphonium ylide was generated *in situ* from dry precursor phosphonium salt in dry THF using NaHMDS or KHMDS as base, followed by addition of aldehyde, which in general was carried out at 20 ºC (in some cases the aldehyde was added at –20 ºC or –78 ºC). The crude product can then be treated in any of the following four ways to result in the separation of phosphine oxide and aldehyde from the alkene product:

(i) The solvent is removed *in vacuo* and oxalyl chloride is added resulting in the evolution of CO and CO_2 gas and, depending on the case, the formation of a pale yellow solid or oil. When bubbling has ceased, cyclohexane is added, and the upper phase formed is decanted off and then filtered.

(ii) Oxalyl chloride is added directly to the reaction mixture (THF solvent) and stirred, causing the evolution of CO and CO_2. When effervescence ceases, the solvent is removed *in vacuo*, cyclohexane is added, and the upper phase formed is decanted off and then filtered.

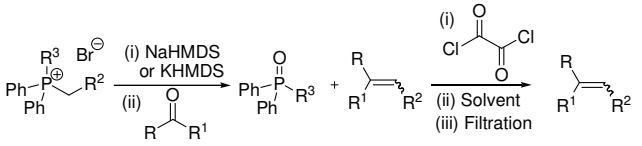
(iii) The solvent is removed *in vacuo*, cyclohexane is added to the crude product, and oxalyl chloride is added, causing CO and CO_2 to be produced. When effervescence ceases, the upper phase formed is decanted off and then filtered.

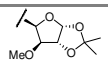
(iv) As in (i), the solvent is removed *in vacuo* and oxalyl chloride is added resulting in the evolution of CO and CO_2 gas.[37] When effervescence ceases, the mixture is cooled to -78 ºC, dry degassed Et_2O is added and the supernatant solution is removed by cannula filtration. To ensure isolation of phosphorus-free alkene, only *ca.* 85% of the supernatant is removed, and the residue is washed three times with dry degassed Et_2O.

In all four methods, the oxalyl chloride reacts with phosphine oxide to form chlorophosphonium salt and release CO and CO_2.[30] The cyclohexane used was not purified, dried or degassed in any way prior to use. The biphasic mixture that forms in the presence of cyclohexane consists of an upper phase of alkene and residual oxalyl chloride dissolved in cyclohexane (this is typically clear or pale yellow), and a solid or viscous oil that sits at the bottom of the vessel. We found, for Wittig reactions that we studied (shown in Table 1), that remaining aldehyde starting material usually does not dissolve in the cyclohexane phase, but stays in the residue along with the chlorophosphonium salt. Washing of the organic solution (after filtration) with aqueous base and then aqueous acid results in the removal of residual oxalyl chloride and also the conjugate acid of the base used to generate the phosphonium ylide (hexamethyldisilylamine in this case), furnishing a high yield of alkene that is free of both phosphorus and aldehyde (Table 1). The use of certain other bases to generate the phosphonium ylide (or indeed using a pre-generated stabilised ylide) would obviate the need for this acid wash.

This journal is © The Royal Society of Chemistry [year]

Table 1. Wittig reactions for which oxalyl chloride treatment of the crude product followed by filtration yields alkene product free of aldehyde and phosphorus.[a] See ESI for full details of the reactions, work-up procedures and analyses.[†]



#	Phosphonium salt		Carbonyl compound		Yield (%)[b]	Alkene *Z/E* Ratio[c]
	R^3	R^2	R	R^1		
1[d]	Ph	*i*-Pr	H		92	100:0
2[e,f]	*i*-Bu	*i*-Pr	H	Ph	93	22:78
3	Me	CO_2Et	H	*c*-C_5H_9	90	10:90
4	Me	Ph	H	*c*-C_5H_9	87	10:90
5	*i*-Bu	*i*-Pr	H	*c*-C_5H_9	96[g]	12:88
6[h]	Ph	*i*-Pr	H	*c*-C_5H_9	96[g]	100:0
7[i,j]	Me	2-$OMeC_6H_4$	H	CH_3	84	15:85
8[i]	Me	2-$OMeC_6H_4$	H	Ph	99	12:88
9[d]	Ph	2-FC_6H_4	H	2-FC_6H_4	93	94:6[j]
10[e]	Me	2-FC_6H_4	H	Ph	96	17:83
11[d,i]	Ph	*i*-Pr	H	2-BrC_6H_4	90	82:18
12[i]	Ph	CO_2t-Bu	H	Ph	87	6:94
13[i]	Ph	CO_2t-Bu	H	2-MeC_6H_4	88	3:97
14[l]	Ph	C(O)Me	H	Ph	87	3:97
15	Me	Ph	Ph	CF_3	92	12:88[j]
16[i]	Ph	CO_2t-Bu	Ph	CF_3	93	15:85

[a] Reaction temperature (at which addition of aldehyde occurred) was 20 ˚C, and the solvent used for the filtration step was cyclohexane, unless otherwise specified.
[b] Based on isolated yield of alkene.
[c] *Z/E* ratio determined by ^{1}H NMR and ^{19}F NMR (where applicable) analysis of the crude product after aqueous work-up.
[d] Reaction (addition of aldehyde) carried out at -78 ˚C.
[e] Filtration was carried out using dry degassed Et_2O at -78 ˚C.
[f] Stated yield takes account of residual aldehyde.
[g] This product could not be completely purified due to decomposition, and was contaminated with a small amount of starting aldehyde. Complete conversion (based on consumption of phosphonium salt) was confirmed by ^{1}H and ^{31}P NMR of the crude product.
[g] Reaction (addition of aldehyde) carried out at -20 ˚C.
[h] Parent phosphine was regenerated from the chlorophosphonium salt contained in the residue after filtration of the alkene solution by dissolving the residue in dry THF and treating with $LiAlH_4$. For entry 7, $MePh_2P$ was isolated in a yield of 98%. For entries 11, 12, 13, and 16, Ph_3P was isolated in yields of 80%, 88%, 95%, and 88% respectively.
[i] Phosphonium chloride salt was used as the ylide pre-cursor.
[j] *Z/E* ratio determined exclusively by ^{19}F NMR analysis of the crude product obtained after aqueous work-up.
[k] Pre-formed commercial ylide acetonylidene-triphenylphosphorane (Aldrich) was used.

From Table 1, it can be seen that this procedure was successful for the removal of triphenylphosphine oxide, *iso*-butyldiphenylphosphine oxide, and methyldiphenylphosphine oxide from Wittig reaction crude products, and is applicable to the crude products of the reactions of all phosphonium ylide types (non-stabilised, semi-stabilised and stabilised) with both aromatic and aliphatic aldehydes, and with ketones. In all cases, comparison of the *Z/E* ratio of the crude alkene product with that of the product after treatment with oxalyl chloride showed it to be unaffected by the procedure.[38] This is particularly striking for the cases of *Z*-2,2'-difluorostilbene (entry 9) and 1-cyclopentyl-3-methylbut-1-ene (entries 5 & 6). The former is known to be extremely sensitive to isomerisation to the *E*-isomer, especially if subjected to column chromatography.[12] The latter alkene (both isomers) spontaneously degrades under ambient conditions simply if allowed to stand. Thus neither alkene is readily accessible in pure form by methods that demand chromatography. The use of our procedure enabled the isolation of each compound in sufficiently pure form for full NMR characterisation, and in particular allowed the very challenging task of establishing the stereochemistry of the isomers of 1-cyclopentyl-3-methylbut-1-ene to be accomplished by the 1D DPFGSE-NOE[39] NMR technique (see ESI for details).[†]

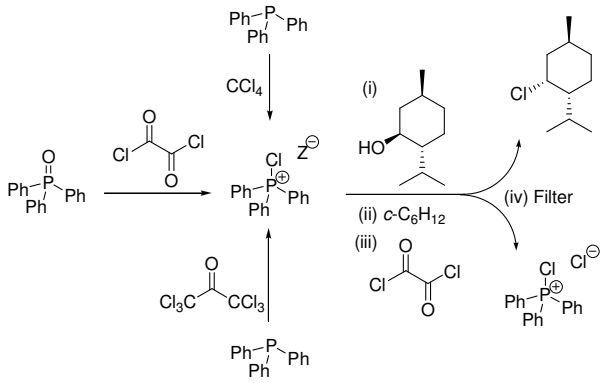
In triphenylphosphine derived cases, the residue remaining after filtration of the cyclohexane solution of alkene was shown to contain the derived CPS by NMR (δ_P = 65 ppm)[34] and frequently also a small amount of aldehyde. On exposure to air this residue was usually found to gradually convert to phosphine oxide over time.

The applicability of this method of purification was also investigated for the product of reactions under Appel and Appel-type conditions. Denton and co-workers[21,22] have used a sequence based on the treatment of phosphine oxide with oxalyl chloride as the basis for their catalytic Appel reactions. They reported that their protocol was less efficient for reactions involving secondary alcohols.[21] Therefore we chose to use menthol in Appel processes to see if our work-up procedure might provide a complementary methodology to theirs (Table 2).

Chlorotriphenylphosphonium salt was generated in three ways: reaction of phosphine with CCl_4 (Table 2 entry 1) or hexachloroacetone (HCA, Table 2, entry 2), and reaction of phosphine oxide with oxalyl chloride (Table 2 entry 3), all in toluene solvent. The salt so formed was treated with menthol and worked up by evaporation of toluene and addition of cyclohexane followed by oxalyl chloride (method (iii) above). After effervescence had ceased, the supernatant liquid was filtered by cannula from the white CPS-containing solid and, after aqueous work-up and evaporation of the cyclohexane, was found to contain neomenthyl chloride in good yield (see Table 2). The absence of any phosphorus-containing material was confirmed by ^{31}P NMR of the product. In the case of Table 2 entry 2, in which HCA was used as the chlorinating agent, the neomenthyl chloride was contaminated with pentachloroacetone.

The use of an alkane solvent or cold Et_2O for the filtration step after chlorophosphonium salt generation is important for the success of the separations achieved in both the Wittig and Appel rections. We have found that the entity generated by treatment of phosphine oxide with oxalyl chloride is at least sparingly soluble in toluene, THF and Et_2O (at 20 ºC), perhaps due to isomerisation between chlorophosphonium salt and dichlorophosphorane.[34] The procedures described above were tested with dry degassed THF (20 ºC) and dry degassed Et_2O (20 ºC) in place of cyclohexane as the filtration solvent. Using these conditions, most of the phosphorus-containing material is successfully removed, but a small quantity of phosphine oxide is invariably present in the product. It may be possible to extend the applicability of the protocol to purification of compounds that are not soluble in cyclohexane by using mixed solvents such as cyclohexane/Et_2O at room temperature.

Table 2. Appel-type reactions for which oxalyl chloride treatment of the crude product followed by filtration yields alkyl chloride product free of phosphorus. [a] See ESI for full details of the reaction, work-up and analyses.[†]



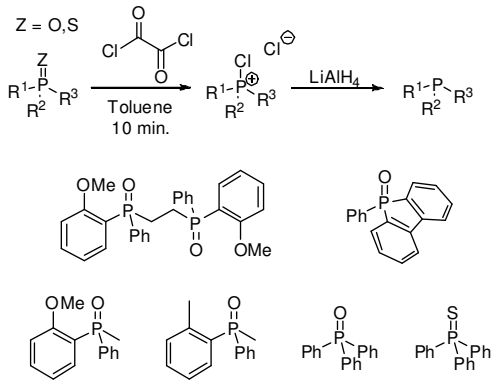
#	CPS Generation	Yield (%) neomenthyl chloride	Yield (%) Ph_3P
1	$Ph_3P + CCl_4$	88	85
2	Ph_3P + HCA[b]	86[c]	92
3	$Ph_3PO + (COCl)_2$	80	86

[a] Yields based on isolated material unless otherwise indicated.
[b] HCA = hexachloroacetone
[c] Yield estimated from ^{1}H NMR of crude product after filtration to remove chlorophosphonium salt. This crude product contains pentachloroacetone (by-product from chlorinating agent).

With a method for isolation of the alkene in hand, we turned our attention to the possibility of reduction of the CPS to phosphine. We were encouraged in this because we had recently discovered that both chlorophosphonium salts and alkoxyphosphonium salts could be subjected to reduction and *in-situ* boranation using $NaBH_4$, thus providing facile conversion from phosphine oxide to phosphine-borane.[32] Drawing on this work and the work of Imamoto and co-workers,[40] we investigated $LiAlH_4$ as reductant, and found it to be successful for the overall reduction of the phosphine chalcogenides shown in Chart 1.

Finally, the separation and phosphine regeneration procedures were combined for a number of Wittig and Appel reactions. Thus the residue remaining after separation of the cyclohexane phase from the insoluble material was dissolved in THF and treated with $LiAlH_4$ at low temperature. The reaction mixture was quenched either by addition of degassed ethyl acetate followed by addition of degassed NH_4Cl solution or by quickly pouring the reaction mixture into a separatory funnel containing a degassed mixture of dichloromethane and aqueous NH_4Cl under inert atmosphere. Standard aqueous work-up (under an oxygen-free atmosphere) followed by solvent removal *in vacuo* furnished the phosphine product.

Chart 1. Phosphine chalcogenides that could be reduced by sequential treatment with oxalyl chloride and $LiAlH_4$.[a]



[a] Full conversion of phosphine chalcogenide to CPS was confirmed by ^{31}P NMR of the reaction mixture. The CPS was reacted with $LiAlH_4$ to give phosphine, which was isolated in high yield. Purity was confirmed by ^{1}H and ^{31}P NMR. See ESI for full details.[†]

In cases where a small amount of phosphine oxide contaminant was shown to be present in the sample of phosphine, elution through a short plug of silica using cyclohexane, ethyl acetate or dichloromethane removed the phosphine oxide and furnished clean phosphine. In general, it was observed that the yield of phosphine was higher and that side-product formation was suppressed if the degassed dichloromethane/NH_4Cl solution work-up was employed. If ordinary bench solvents containing dissolved oxygen are used for the work-up then a very significant amount of phosphine oxide is formed. The high yields of regenerated phosphine from the Wittig and Appel-type reactions (where applicable) are shown in Table 1 (entries 7, 11, 12, 13, and 16 – see footnote *i*) and Table 2 (all entries) respectively. For phosphine regeneration from Wittig reactions, the best results were obtained if the *initial* crude product was subjected to aqueous work-up (before any oxalyl chloride addition) using dichloromethane as the organic solvent. This removed inorganic salts and products derived from the hexamethyldisilazide base, while ensuring that all phosphine oxide (much of it derived from

This journal is © The Royal Society of Chemistry [year]

the Wittig reaction, but some also from hydrolysis of unreacted ylide or phosphonium salt) remained present in the crude product after the aqueous work-up. In some cases, the mixture produced by the addition of degassed ethyl acetate to the THF solution of phosphine and $LiAlH_4$ (after reduction of the chlorophosphonium salt) was observed to contain small quantities of unreacted phosphonium salt starting material by ^{31}P NMR. In these instances, the mixture was filtered prior to the work-up with degassed NH_4Cl solution, since phosphonium salt hydrolysis would result in contamination of the phosphine product with phosphine oxide.

Conclusions

We have reported a short procedure that, in principle, can be used to remove the phosphine oxide by-product from any Wittig or Appel reaction, so long as the respective alkenes or alkyl chlorides are soluble in cyclohexane (or other alkanes) or cold diethyl ether. It may also be applied to remove most of the phosphine oxide if the alkene/alkyl chloride is soluble in diethyl ether (at room temperature) or THF, especially if the filtrations are carried out at low temperature. The method allows the clean isolation of alkenes that are very sensitive either to *Z/E* isomerisation and/or polymerisation. Therefore it is potentially extremely useful preparatively.

Thus the troublesome problem of phosphine oxide removal may be easily circumvented without having to resort to modification of the starting materials. We envisage that the method can also be applied to other reactions where phosphine oxide removal is a problem e.g. the Mitsunobu & Staudinger reactions.

We have also noted that the phosphine used for the Wittig or Appel reaction can be regenerated from the crude separated chlorophosphonium salt by treatement with $LiAlH_4$ as reductant. This is not significant for the case of triphenylphosphine but could be most advantageous for cases where a non-standard phosphine has to be used in the Wittig reaction.

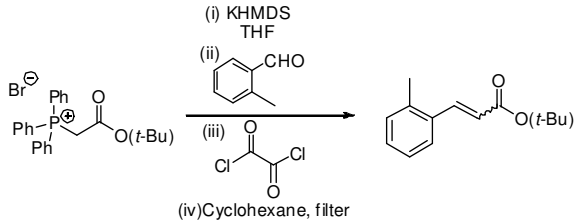
Acknowledgements

We thank sincerely the Irish Research Council for Science, Engineering and Technology (IRCSET) for an EMBARK Scholarship to PAB and Science Foundation Ireland (SFI) for a scholarship to KVR (under grants 08/RFP/CHE1251 and 09/IN.1/B2627). We are also very grateful to UCD Centre for Synthesis and Chemical Biology (CSCB) and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities and especially to Dr. Yannick Ortin for NMR.

Experimental

Representative experimental procedures for the Wittig Appel reactions, phosphine oxide removal and phosphine regeneration are given below. For details of the other reactions in Tables 1 and 2 and Chart 1 see the ESI.[†]

Synthesis & purification of *tert*-butyl 3-(2-methylphenyl)prop-2-enoate (Table 1 entry 13).



(*tert*-Butoxycarbonylmethyl)triphenylphosphonium bromide (328 mg, 0.794 mmol) and KHMDS (167 mg, 0.834 mmol) were added to a flame-dried Schlenk flask under an atmosphere of argon in a glove box. The Schlenk flask was attached to a Schlenk manifold and charged with nitrogen by the standard pump-and-fill technique.[41] Dry THF (4 ml) was added, and the resulting mixture was stirred for one hour at 20 ºC. 2-methylbenzaldehyde (95 mg, 0.79 mmol) was added by nitrogen-flushed syringe. The reaction mixture was stirred for 12 hours. The THF solvent was removed *in vacuo*. A small sample was removed for analysis by NMR (*Z/E* ratio of alkene in crude product was 3:97). The residue was dissolved in CH_2Cl_2 (15 ml) and washed with saturated NH_4Cl solution (5 ml). The phases were separated, and the aqueous phase was washed twice with CH_2Cl_2 (10 ml each). The combined isolated CH_2Cl_2 phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

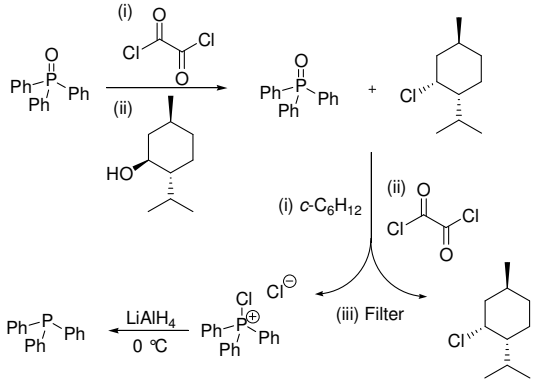
Oxalyl chloride (0.10 ml, 1.2 mmol) was added to the residue, causing the formation of a pale yellow solid. Cyclohexane (10 ml) was added, and after swirling of the mixture, the liquid was decanted off. The residue was washed a further five times in this manner with cyclohexane (5 ml). The combined cyclohexane phases were filtered through a cannula using Whatman grade GFD glass microfibre filter paper. The filtered solution was washed with saturated $NaHCO_3$ solution (2 x 5 ml) and aqueous HCl solution (1M, 2 x 5 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield the phosphorus-free alkene (0.15 g, 88%), as confirmed by ^1H and ^{31}P NMR. The *Z/E* ratio of the alkene was determined to be 3:97 by comparison of the relative integrations of the signals assigned to each isomer.

^1H NMR of purified product (integrations relative to 1 H of *E*-isomer): δ_H (500 MHz, $CDCl_3$) 7.88 (1 H, d, *J* 15.9, *E*-H-3), 7.55-7.53 (1 H, m, *E*-ArH), 7.27 – 7.22 (contains $CHCl_3$ signal, m, *E*-ArH), 7.21-7.16 (2 H, m, *E*-ArH), 7.02 (0.03 H, d, *J* 12.1, *Z*-H-3), 6.29 (1 H, d, *J* 15.9, *E*-H-2), 5.95 (0.03 H, d, *J* 12.1, *Z*-H-2), 2.43 (3 H, s, *E*-CH_3), 2.27 (0.1 H, s, *Z*-CH_3), 1.54 (9 H, s, *E*-$C(CH_3)_3$), 1.30 (0.27 H, s, *Z*- $C(CH_3)_3$). [42]

The Schlenk flask containing the residue from the filtration was charged with nitrogen. Dry THF (2 ml) was added, and the resulting mixture was cooled to – 78 ºC and $LiAlH_4$ in THF (1M,

1.2 ml, 1.2 mmol) was added dropwise, resulting in the evolution of hydrogen gas and the dissolution of all of the solid material in the THF. The reaction mixture was removed from the cold bath and stirred for 10 minutes, then quickly poured into a degassed mixture of CH_2Cl_2 (30 ml) and saturated NH_4Cl solution (15 ml) contained in a separatory funnel under an inert atmosphere. After swirling, the CH_2Cl_2 phase was allowed to drain off. The aqueous phase was extracted with further degassed CH_2Cl_2 (15 ml). The combined CH_2Cl_2 phases were dried over $MgSO_4$ and filtered. The solvent was removed under vacuum yielding clean Ph_3P (0.20 g , 95%), δ_P (121 MHz, $CDCl_3$) -5.3 (lit.[43] -4.8).

Reaction of triphenylphosphine oxide + oxalyl chloride + (-)-menthol (Table 2 entry 3).



Triphenylphosphine oxide (1.0 g, 3.5 mmol) was dissolved in dichloromethane (10 ml) in a flame dried Schlenk tube under an atmosphere of nitrogen. Oxalyl chloride (0.30 mL, 3.5 mmol) was added dropwise to the reaction mixture resulting in the formation of a white precipitate. (^{31}P NMR δ 64.5 ppm). (-)-Menthol (0.56 g, 3.5 mmol) was added to the reaction mixture through a powder funnel, causing the reaction mixture to become clear. The complete formation of alkoxyphosphonium salt was confirmed by ^{31}P NMR of a small sample of the reaction mixture (^{31}P NMR δ 58.9). The reaction was allowed to stir for 30 minutes. Completion of the reaction was confirmed by ^{31}P NMR analysis of a small sample of the reaction mixture (^{31}P NMR δ 25.2). The toluene reaction solvent was removed *in vacuo* and cyclohexane (10 mL) was added to the residue. Oxalyl chloride (0.30 mL, 3.5 mmol) was added dropwise to the reaction mixture which caused the formation of a white precipitate of chlorophosphonium salt. The supernatant liquid was removed by cannula filtration. The residue was washed (2x 10 mL) twice with cyclohexane and the washings removed by cannula filtration. The combined cyclohexane filtrate was washed with water (20 mL x 2). The separated organic phase was then dried over anhydrous $MgSO_4$. Filtration to remove the drying agent and evaporation of the solvent *in vacuo* yielded neomenthyl chloride (0.49 g, 80 %).

δ_H (300 MHz, $CDCl_3$, 25 °C): 4.77 (m, 1 H), 2.02–1.91 (m, 1H), 1.88–1.78 (m, 1 H),1.68–1.56 (m, 2H), 1.48–1.39(m, 2H), 1.33–1.28 (m, 2H), 1.04–1.01 (m, 1H) 0.85 (d, $^3J_{H,H}$ = 6.4 Hz, 3H, CH_3), 0.83 (d, $^3J_{H,H}$ = 6.7 Hz, 3H, CH_3), 0.70 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH_3).[44]

The solid residue remaining after cannula filtration of the reaction mixture was dissolved in THF (10 ml) and cooled to 0 ˚C. A solution of $LiAlH_4$ in THF (1.0M, 3.5 mL, 3.5 mmol) was added dropwise to the mixture, which was then stirred for 30 minutes while warming to room temperature. Ethyl acetate (10 ml) was added to quench the $LiAlH_4$, followed by saturated aqueous NH_4Cl (10 ml). The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was washed twice more with ethyl acetate (10 ml each wash). The combined organic phases were dried over $MgSO_4$, filtered through a silica plug to remove residual phosphine oxide and concentrated *in vacuo* to give phosphine. (0.78 g, 86 %). δ_P (162 MHz): -4.5 (lit.[43] -4.8).

Notes and references

[a] *Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland*
Tel: +353-1-7162308; Fax: +353-1-7162127
Mail to: declan.gilheany@ucd.ie

† Electronic Supplementary Information (ESI) available: [Experimental procedures and characterization data for alkenes, alkyl chlorides and phosphines]. See DOI: 10.1039/b000000x

1 (a) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863; (b) A. W. Johnson, *Ylides and Imines of Phosphorus*, Wiley, New York, 1993, pp. 221-305; (c) E. Vedejs, M. J. Peterson in *Topics in Stereochemistry*, eds. E. L Eliel & S. H. Wilen, Wiley, New York, 1994; Vol. 21, pp. 1-158; (d) A. D. Abell, M. K. Edmonds in *Organophosphorus Reagents*, ed. P. J. Murphy, Oxford University Press, Oxford, U.K., 2004, pp. 99-127; (e) R. Schobert in *Organophosphorus Reagents*; ed. P. J. Murphy, Oxford University Press, Oxford, U.K., pp. 12-148; (f) A. D. Abell, M. K. Edmonds in *Modern Carbonyl Olefination*, ed. T. Takeda, Wiley-VCH, Weinheim, Germany, 2004, pp. 1-17; (g) E. Vedejs, M. J. Peterson in *Advances in Carbanion Chemistry*; ed. V. Snieckus, JAI, Greenwich, CN, 1996, Vol. 2, pp. 1-85.

2 (a) R. Appel, M. Halstenberg in *Organophosphorus Reagents in Organic Synthesis*, ed. J. I. G. Cadogan, Academic Press, London, 1979, pp. 387-431; (b) R. Appel, *Angew. Chem., Int. Ed.*, 1975, **14**, 801; (c) I. M. Downie, J. B. Holmes, J. B. Lee, *Chem. Ind. (London)* 1966, 900.

3 (a) O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* 1967, **40**, 2380.; (b) T. Mukaiyama, R. Matsueda, H. Maruyama, *Bull. Chem. Soc. Jpn.* 1970, **43**, 1271; (c) D. L. Hughes in *Organic Reactions*, eds. P. Beak *et al.*, Wiley, New York, 1992, Vol. 42, pp. 335-656; (d) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* 2009, **109**, 2551; (e) O. Mitsunobu, *Synthesis*, 1981, 1; (f) S. Dandapani, D. P. Curran, *Chem. Eur. J.* 2004, **10**, 3130.

4 (a) See reference 1b; (b) F. Palacios, C, Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, *Tetrahedron*, 2007, **63**, 523.

5 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* 2007, **9**, 411 – 420.

6 J. J. Cao, F. Zhou, J. Zhou, *Angew. Chem. Int. Ed.* 2010, **49**, 4976.

7 See reference 3f.

8 I. J. S. Fairlamb, *ChemSusChem.* 2009, **2**, 1021.

9 D. Stockburger in *Production-Integrated Environmental Protection and Waste Management in the Chemical Industry*, ed. C. Christ, Wiley-VCH, Weinheim, Germany, 1999, pp. 90-93.

10 H. Pommer, A. Nürrenbach, *Pure Appl. Chem.*1975, **43**, 527.

11 T. Fukumoto, A. Yamamoto, US Patent 5292973, March 8th 1994, *Chem. Abs.* 1994: 533844; CAN **121**:133844.

12 E. C. Dunne, E. J. Coyne, P. B. Crowley, D. G. Gilheany, *Tetrahedron Lett.,* 2002, **43**, 2449.

13 J. McNulty, K. Keskar, *Tetrahedron Lett.* 2008, **49**, 7054.

This journal is © The Royal Society of Chemistry [year]

14 Q. Wang, M. Khoury, M. Schlosser, *Chem. Eur. J,* 2000, **6**, 420; S. Trippet, D. M. Walker, *J. Chem. Soc.* 1961, 2130; H. Daniel, M. Le Corre, *Tetrahedron Lett.*, 1987, **28**, 1165.
15 M. G. Russell, S. Warren, *Tetrahedron Lett.* 1998, **39**, 7995.
16 J. McNulty, P. Das, *Eur. J. Org. Chem.* 2009, 4031.
17 F. Westman, *Org. Lett.* 2001, **3**, 3745.
18 P. S.-W. Leung, Y. Teng, P. H. Toy, *Synlett*, 2010, 1997.
19 P. S.-W. Leung, Y. Teng, P. H. Toy, *Org. Lett.*, 2010, **12**, 4996.
20 C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, G. C. Chass, *Angew. Chem. Int. Ed.*, 2009, **48**, 6836. See also reference 8 for a review on the topic of the phosphine-catalysed Wittig reaction.
21 R. M. Denton, J. An, B. Adeniran, *Chem. Commun.,* 2010, **46**, 3025-3027.
22 R. M. Denton, J. An, B. Aderinan, A, J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* 2011, **76**, 6749.
23 H. A. van Kalkeren, S. H. A. M. Leenders, C. R. A. Hommersom, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Eur. J.* 2011, **17**, 11290.
24 R. M. Denton, X. Tang, A. Przeslak, *Org. Lett.* 2010, **12**, 4678.
25 S. P. Marsden, A. E. McGonagle, B. McKeever-Abbas, *Org.Lett.,* 2008, **10**, 2589.
26 T. Yano, M. Hoshino, M. Kuroboshi, H. Tanaka, *Synlett* 2010, 801.
27 T. Yano, M. Hoshino, H. Tanaka, *Tetrahedron Lett.* 2010, **51**, 698.
28 C. Harcken, S. F. Martin, *Org. Lett.* 2001, **3**, 3591.
29 J. Cotter, A.-M. L. Hogan, D. F. O'Shea, *Org. Lett.,* 2007, **9**, 1493.
30 M. Masaki, K. Fukui, *Chem. Lett.*, 1977, 151-152; K. Fukui, N. Kakeya, U. S. Patent 4,301,301, 1981.
31 E. Bergin, C. T. O'Connor, S. B. Robinson, E. M. McGarrigle,; C. P. O'Mahony, D. G. Gilheany, *J. Am. Chem. Soc.* 2007, **129**, 9566.
32 K. V. Rajendran, D. G. Gilheany, *Chem. Commun.* 2012, **48**, 817.
33 S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *Chem. Commun.,* 1996, 2521.
34 S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *Chem. Commun.,* 1998, 921.
35 M. A. H. A. Al-Juboori, P. N. Gates, A. S. Muir, *J. Chem. Soc. Chem. Commun.* **1991**, 1271.
36 N. C. Gonnella, C. Busacca, S. Campbell, M. Eriksson, N. Grinberg, T. Bartholomeyzik, S. Ma, D. L. Norwood, *Magn. Reson. Chem.,* 2009, **47**, 461.
37 For cases where the Wittig reaction is performed in Et_2O, it was found in practice that the reproducibility of phosphorus removal was far superior if the oxalyl chloride was added to the neat crude product rather than to the solution of the crude product in Et_2O.
38 The *Z*/*E* ratio of the alkene was assigned by integration of characteristic signals in the ^{1}H NMR and/or ^{19}F NMR, for both the crude and the purified products.
39 DPFGSE-NOE stands for Double Pulse Field Gradient Spin Echo Nuclear Overhauser Effect NMR spectroscopy.
40 T. Imamoto, S. Kikuchi, T. Miura, Y. Wada, *Org. Lett.*. 2001, **3**, 87-90.
41 D. F. Shriver, M. A. Drezdzon, *The Manipulation of Air Sensitive Compounds*, 2nd edn., McGraw-Hill, New York, 1986.
42 K. S. Yoo, C. H. Yoon, K. W. Jung, *J. Am. Chem. Soc.* 2006, **128**, 16384. *E*-isomer of alkene.
43 T. Ramnial, S. A. Taylor, M. L. Bender, B. Gorodetsky, P. T. K. Lee, D. A. Dickie, B. M. McCollum, C. C. Pye, C. J. Walsby, J. A. C. Clyburne, *J. Org. Chem.* 2008**, 73**, 801.
44 Ścianowski, J.; Rafiński, Z.; Wojtczak, A. *Eur. J. Org. Chem.* 2006, 3216.